# EU Clinical Trials Register

## Clinical trial results:

## A Prospective Randomized Placebo Controlled Study to Evaluate the Effect of Celecoxib on the Efficacy and Safety of Amlodipine on Renal and Vascular Function in Subjects with Existing Hypertension Requiring Antihypertensive Therapy

### Summary

| | |
|---|---|
| EudraCT number | 2016-002214-47 |
| Trial protocol | GB |
| Global end of trial date | 21 July 2017 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 10 October 2018 |
| First version publication date | 10 October 2018 |

### Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | KIT-302-03-02 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02979197 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Kitov Pharma Ltd |
| Sponsor organisation address | One Azrieli Center, Round Tower, Floor 19, 132 Menachem Begin Road , Tel Aviv, Israel, 6701101 |
| Public contact | Chief Medical Officer/US Agent, Kitov Pharma Ltd, 001 2029652215, paul@kitovpharma.com |
| Scientific contact | Chief Medical Officer/US Agent, Kitov Pharma Ltd, 001 2029652215, paul@kitovpharma.com |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 21 July 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 21 July 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 21 July 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate that the mean reduction in average daytime (9:00 to 21:00) ambulatory systolic blood pressure (SBPday) after oral administration of amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together once a day (qd) for 14 days in adult subjects with existing hypertension is no less than half the mean reduction in SBPday after oral administration of amlodipine tablets (10 mg) given alone (i.e., with matched celecoxib placebo) qd for 14 days in the same population.

Protection of trial subjects:

This study was in compliance with the ethical principles derived from the principles of Good Clinical Practice (GCP) [current International Conference of Harmonization (ICH) guidelines], and the Declaration of Helsinki (1964) including all amendments up to and including the October 2013 revision.

All local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

The safety assessments included clinical laboratory tests (hematology, serum chemistry and urinalysis), Electrocardiogram, Physical examination findings, Orthostatic Hypotension measurements and Vital signs. Adverse events were monitored throughout the study.

| | |
|---|---|
| Background therapy: | |
| None | |
| Evidence for comparator: - | |
| Actual start date of recruitment | 03 November 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 105 |
| Worldwide total number of subjects | 105 |
| EEA total number of subjects | 105 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |

| | |
|---|---|
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 89 |
| From 65 to 84 years | 16 |
| 85 years and over | 0 |

# Subject disposition

## Recruitment

Recruitment details:

This study was conducted across 9 sites in the United Kingdom. The first patient first visit was on the 3rd November 2016. The last patient last visit was on the 21st July 2017.

## Pre-assignment

Screening details:

Subjects underwent assessments to determine eligibility at the Initial Screening Visit (Day -14 to -10; 255 subjects), Final Screening Visit (Day -1; 159 subjects), and the morning prior to randomization (Study Day 0; 154 subjects). A total of 150 subjects were screen failures and the remaining 105 were randomized.

## Period 1

| Period 1 title | Overall trial (overall period) |
|---|---|
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Assessor |

Blinding implementation details:

Blinding of the subject and Investigational staff to treatment was achieved by using over-encapsulated (OE) formulations and matched placebo capsules. The appearance of the OE amlodipine tablets and matched placebo capsules were identical. Similarly, the appearance of the OE celecoxib capsules and matched placebo capsules were identical. Each patient kit, and the 2 bottles of study drug within the kit, were labeled in a manner to maintain blinding of the subject and Investigational staff.

## Arms

| Are arms mutually exclusive? | Yes |
|---|---|
| **Arm title** | Amlodipine+Celecoxib |

Arm description:

Over-encapsulated 10 mg amlodipine besylate tablet + over-encapsulated 200 mg celecoxib capsule once a day for two weeks

Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Over-encapsulated 200 mg celecoxib capsule: Over-encapsulated 200 mg celecoxib capsule once a day for two weeks

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | OE 10mg amlodipine besylate tablet |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

| Investigational medicinal product name | OE 200mg celecoxib capsule |
|---|---|
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Over-encapsulated 200 mg celecoxib capsule once a day for two weeks

| **Arm title** | Amlodipine+Placebo |
|---|---|

Arm description:

Over-encapsulated 10 mg amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

| Arm type | Active comparator |
|---|---|
| Investigational medicinal product name | OE 10mg amlodipine besylate tablet |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

| Investigational medicinal product name | Matched placebo capsule for OE celecoxib capsule |
|---|---|
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

| **Arm title** | Placebo+Placebo |
|---|---|

Arm description:

Matched placebo capsule for over-encapsulated amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Matched placebo capsule for over-encapsulated amlodipine besylate tablet: Matched placebo capsule for over-encapsulated amlodipine besylate tablet once a day for two weeks

| Arm type | Sham comparator |
|---|---|
| Investigational medicinal product name | Matched placebo capsule for OE celecoxib capsule |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

| Investigational medicinal product name | Matched placebo capsule for OE amlodipine tablet |
|---|---|
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Matched placebo capsule for over-encapsulated amlodipine besylate tablet once a day for two weeks

| Number of subjects in period 1 | Amlodipine+Celecoxib | Amlodipine+Placebo | Placebo+Placebo |
|---|---|---|---|
| Started | 48 | 49 | 8 |
| Completed | 44 | 45 | 8 |
| Not completed | 4 | 4 | 0 |
|     Subject unable to commit to study dates | - | 1 | - |
|     Adverse event, non-fatal | 4 | 2 | - |
|     Protocol deviation | - | 1 | - |

| | Amlodipine+Celecoxib | Amlodipine+Placebo | Placebo+Placebo |
|---|---|---|---|
| Started | 48 | 49 | 8 |
| Completed | 44 | 45 | 8 |
| Not completed | 4 | 4 | |

## Baseline characteristics

### Reporting groups

| Reporting group title | Amlodipine+Celecoxib |
|---|---|

Reporting group description:

Over-encapsulated 10 mg amlodipine besylate tablet + over-encapsulated 200 mg celecoxib capsule once a day for two weeks

Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Over-encapsulated 200 mg celecoxib capsule: Over-encapsulated 200 mg celecoxib capsule once a day for two weeks

| Reporting group title | Amlodipine+Placebo |
|---|---|

Reporting group description:

Over-encapsulated 10 mg amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

| Reporting group title | Placebo+Placebo |
|---|---|

Reporting group description:

Matched placebo capsule for over-encapsulated amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Matched placebo capsule for over-encapsulated amlodipine besylate tablet: Matched placebo capsule for over-encapsulated amlodipine besylate tablet once a day for two weeks

| Reporting group values | Amlodipine+Celecoxib | Amlodipine+Placebo | Placebo+Placebo |
|---|---|---|---|
| Number of subjects | 48 | 49 | 8 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 42 | 39 | 8 |
| From 65-84 years | 6 | 10 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 55.5 | 56.7 | 52.5 |
| standard deviation | ± 7.13 | ± 7.43 | ± 7.84 |

| Gender categorical | | | |
|---|---|---|---|
| Units: Subjects | | | |
|     Female | 17 | 18 | 4 |
|     Male | 31 | 31 | 4 |
| Race | | | |
| Units: Subjects | | | |
|     American Indian or Alaska Native | 0 | 0 | 0 |
|     Asian | 0 | 1 | 1 |
|     Black or African American | 1 | 0 | 0 |
|     White | 46 | 47 | 7 |
|     More than one race | 1 | 1 | 0 |
|     Unkown or not reported | 0 | 0 | 0 |
|     Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Region of Enrollment | | | |
| Units: Subjects | | | |
|     United Kingdom | 48 | 49 | 8 |
| Average daytime (9:00 to 21:00) ambulatory systolic blood pressure measured at Day -1 | | | |
| Units: mmHg | | | |
|     arithmetic mean | 148.0 | 150.0 | 151.5 |
|     standard deviation | ± 7.95 | ± 8.25 | ± 10.91 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 105 | | |
| Age categorical | | | |
| Units: Subjects | | | |
|     In utero | 0 | | |
|     Preterm newborn infants (gestational age < 37 wks) | 0 | | |
|     Newborns (0-27 days) | 0 | | |
|     Infants and toddlers (28 days-23 months) | 0 | | |
|     Children (2-11 years) | 0 | | |
|     Adolescents (12-17 years) | 0 | | |
|     Adults (18-64 years) | 89 | | |
|     From 65-84 years | 16 | | |
|     85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
|     arithmetic mean | | | |
|     standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
|     Female | 39 | | |
|     Male | 66 | | |
| Race | | | |
| Units: Subjects | | | |
|     American Indian or Alaska Native | 0 | | |
|     Asian | 2 | | |
|     Black or African American | 1 | | |
|     White | 100 | | |

| | | | |
|---|---|---|---|
| More than one race | 2 | | |
| Unkown or not reported | 0 | | |
| Native Hawaiian or Other Pacific Islander | 0 | | |
| **Region of Enrollment**<br>Units: Subjects | | | |
| United Kingdom | 105 | | |
| Average daytime (9:00 to 21:00) ambulatory systolic blood pressure measured at Day -1<br>Units: mmHg<br>arithmetic mean<br>standard deviation | - | | |

# End points

## End points reporting groups

| Reporting group title | Amlodipine+Celecoxib |
|---|---|

Reporting group description:

Over-encapsulated 10 mg amlodipine besylate tablet + over-encapsulated 200 mg celecoxib capsule once a day for two weeks

Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Over-encapsulated 200 mg celecoxib capsule: Over-encapsulated 200 mg celecoxib capsule once a day for two weeks

| Reporting group title | Amlodipine+Placebo |
|---|---|

Reporting group description:

Over-encapsulated 10 mg amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

| Reporting group title | Placebo+Placebo |
|---|---|

Reporting group description:

Matched placebo capsule for over-encapsulated amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Matched placebo capsule for over-encapsulated amlodipine besylate tablet: Matched placebo capsule for over-encapsulated amlodipine besylate tablet once a day for two weeks

## Primary: Mean Reduction in Average Daytime (9:00 to 21:00) Ambulatory Systolic Blood Pressure (SBPday)

| End point title | Mean Reduction in Average Daytime (9:00 to 21:00) Ambulatory Systolic Blood Pressure (SBPday)[1] |
|---|---|

End point description:

Intent-to-treat (ITT) population = all randomized subjects with a valid Baseline (Day -1 to Day 0) ambulatory blood pressure monitor (ABPM) measurement.
For efficacy analyses, the validity of ABPM measurements was based on valid daytime measurements.

| End point type | Primary |
|---|---|

End point timeframe:

Baseline and 14 days

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Per protocol, the primary endpoint was the difference in the mean reduction in SBPday from baseline to final measurement between the Amlodipine+Celecoxib and Amlodipine+Placebo arms. A comparison with the Placebo+Placebo arm was not part of the primary endpoint and therefore is not included.

| End point values | Amlodipine+Celecoxib | Amlodipine+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 48 | 48 | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | -8.0 (± 8.24) | -9.8 (± 8.89) | | |

## Statistical analyses

| Statistical analysis title | StatsAnalysis1 Mean Reduction in Average SBPday |
|---|---|

Statistical analysis description:

Last observation carried forward (LOCF) method was used. Primary efficacy analysis was based on the difference between the Amlodipine+Celecoxib and Amlodipine+Placebo (arms 1 and 2, respectively) in the mean reduction in SBPday from baseline (Day -1) to final (Day 13), where a subject completed the 14-day treatment plan, or to Day 6, where a subject was withdrawn from treatment before the Day 13 dose but after the Day 6 dose, or to baseline, where a subject was withdrawn before the Day 6 dose.

| Comparison groups | Amlodipine+Celecoxib v Amlodipine+Placebo |
|---|---|
| Number of subjects included in analysis | 96 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[2] |
| P-value | = 0.024 |
| Method | t-test, 2-sided |

Notes:

[2] - A two-sample t-test was used to test the one-sided hypothesis that treatment with Amlodipine+Celecoxib (arm 1) was non-inferior to half of the effect achieved with Amlodipine+Placebo (arm 2). The primary efficacy endpoint was considered met if the lower limits of the 97.5% one-side confidence interval (CI) for the difference in SBPday reduction in arm 1 and 50% of the mean reduction in arm 2 was less than 0.

## Secondary: Mean Change in Body Weight

| End point title | Mean Change in Body Weight |
|---|---|

End point description:

ITT population as described for primary outcome

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline and 14 days

| End point values | Amlodipine+Celecoxib | Amlodipine+Placebo | Placebo+Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48 | 48 | 8 | |
| Units: Kg | | | | |
| arithmetic mean (standard deviation) | 0.3 (± 1.02) | -0.3 (± 1.03) | -1.5 (± 3.95) | |

## Statistical analyses

| Statistical analysis title | StatsAnalysis1 Mean Change in Body Weight |
|---|---|

Statistical analysis description:

A serial gatekeeping strategy was used for the secondary efficacy analyses. If, and only if, statistical significance was achieved for the primary efficacy endpoint (SBPday), a secondary hierarchical analysis was to be used to evaluate the secondary efficacy endpoints and was only to proceed from one secondary efficacy endpoint to the next if the alpha was met for the prior analyses. Mean change in body weight was the 1st of the four secondary efficacy endpoints. LOCF technique was used.

| Comparison groups | Amlodipine+Celecoxib v Amlodipine+Placebo v Placebo+Placebo |
|---|---|
| Number of subjects included in analysis | 104 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[3] |
| P-value | = 0.006 [4] |
| Method | ANOVA |

Notes:

[3] - Analysis of variance (ANOVA) was used to compare the mean changes in body weight from baseline to end of treatment among the three treatment arms. The omni-bus test was to conclude if any differences existed, with post-hoc comparisons identifying specific differences between treatment arms. Any statistically significant differences would be sufficient to pass this gate in the study-wide gate keeping strategy.

[4] - While the ANOVA showed a statistically significant difference between the three treatment arms (p=0.006), the pairwise comparisons of the treatment arms did not show any clinically meaningful differences.

## Secondary: Mean Reduction in Average 24-hour Ambulatory Systolic Blood Pressure (SBP24h)

| End point title | Mean Reduction in Average 24-hour Ambulatory Systolic Blood Pressure (SBP24h)[5] |
|---|---|

End point description:

ITT population as described for primary outcome

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline and 14 days

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Per protocol, the secondary endpoint related to SBP24hr was the difference in the mean reduction in SBP24hr from baseline to final measurement between the Amlodipine+Celecoxib and Amlodipine+Placebo arms. A comparison with the Placebo+Placebo arm was not part of this secondary endpoint and therefore is not included.

| End point values | Amlodipine+Celecoxib | Amlodipine+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 48 | 48 | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | -8.2 (± 7.80) | -8.5 (± 8.47) | | |

## Statistical analyses

| Statistical analysis title | StatsAnalysis1 Mean Reduction in Average SBP24h |
|---|---|

Statistical analysis description:

A serial gatekeeping strategy was used for the secondary efficacy analyses. If, and only if, statistical significance was achieved for the primary efficacy endpoint (SBPday), a secondary hierarchical analysis was to be used to evaluate the secondary efficacy endpoints and was only to proceed from one secondary efficacy endpoint to the next if the alpha was met for the prior analyses. Mean reduction in

SBP24h was the 2nd of the four secondary efficacy endpoints. LOCF technique was used.

| Comparison groups | Amlodipine+Celecoxib v Amlodipine+Placebo |
|---|---|
| Number of subjects included in analysis | 96 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[6] |
| P-value | = 0.826 |
| Method | t-test, 2-sided |

Notes:

[6] - A two-sample t-test for superiority was used to test the one-sided hypothesis that treatment with Amlodipine+Celecoxib lowered SBP24h to a greater degree than Amlodipine+Placebo.

## Secondary: Mean Reduction in Average 24-hour Ambulatory Diastolic Blood Pressure (DBP24h)

| End point title | Mean Reduction in Average 24-hour Ambulatory Diastolic Blood Pressure (DBP24h)[7] |
|---|---|

End point description:

ITT population as described for primary outcome

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline and 14 days

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Per protocol, the secondary endpoint related to DBP24hr was the difference in the mean reduction in DBP24hr from baseline to final measurement between the Amlodipine+Celecoxib and Amlodipine+Placebo arms. A comparison with the Placebo+Placebo arm was not part of this secondary endpoint and therefore is not included.

| End point values | Amlodipine+Celecoxib | Amlodipine+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 48 | 48 | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | -4.4 (± 4.68) | -3.8 (± 5.27) | | |

## Statistical analyses

| **Statistical analysis title** | StatsAnalysis1 Mean Reduction in Average DBP24h |
|---|---|

Statistical analysis description:

A serial gatekeeping strategy was used for the secondary efficacy analyses. If, and only if, statistical significance was achieved for the primary efficacy endpoint (SBPday), a secondary hierarchical analysis was to be used to evaluate the secondary efficacy endpoints and was only to proceed from one secondary efficacy endpoint to the next if the alpha was met for the prior analyses. Mean reduction in DBP24h was the 3rd of the four secondary efficacy endpoints. LOCF technique was used.

| Comparison groups | Amlodipine+Celecoxib v Amlodipine+Placebo |
|---|---|
| Number of subjects included in analysis | 96 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[8] |
| P-value | = 0.5 |
| Method | t-test, 2-sided |

Notes:

[8] - A two-sample t-test for superiority was used to test the one-sided hypothesis that treatment with Amlodipine+Celecoxib lowered DBP24h to a greater degree than Amlodipine+Placebo. Note, although the alpha was not met for the SBP24h efficacy endpoint of the serial gate-keeping strategy, DBP24h was

still evaluated for informational purposes and the results are presented here.

## Secondary: Mean Change in Creatinine Clearance

| End point title | Mean Change in Creatinine Clearance[9] |
|---|---|

End point description:

ITT population as described for primary outcome

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline and 14 days

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Renal function was analyzed by evaluating the decreases in mean serum creatinine from baseline to Day 14 WITHIN EACH TREATMENT ARM, as well as BETWEEN TREATMENT ARMS. The within arm comparisons (i.e., mean decrease from baseline to Day 14) were conducted as three separate analyses, one for each of the three treatment arms. The between treatment arm comparisons (i.e., mean decrease from baseline to Day 14 between arms) were conducted as three separate PAIRWISE comparisons.

| End point values | Amlodipine+Celecoxib | Amlodipine+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 48 | 48 | | |
| Units: mL/min | | | | |
| arithmetic mean (standard deviation) | 4.9 (± 10.62) | 3.4 (± 20.96) | | |

### Statistical analyses

| **Statistical analysis title** | StatsAnalysis1 Mean Change in Creatinine Clearance |
|---|---|

Statistical analysis description:

A serial gatekeeping strategy was used for the secondary efficacy analyses. If, and only if, statistical significance was achieved for the primary efficacy endpoint (SBPday), a secondary hierarchical analysis was to be used to evaluate the secondary efficacy endpoints and was only to proceed from one secondary efficacy endpoint to the next if the alpha was met for the prior analyses. Mean change in creatinine clearance was the 4th of the 4 secondary efficacy endpoints. LOCF technique was used.

| Comparison groups | Amlodipine+Celecoxib v Amlodipine+Placebo |
|---|---|
| Number of subjects included in analysis | 96 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[10] |
| P-value | = 0.668 [11] |
| Method | t-test, 2-sided |

Notes:

[10] - A two-sample t-test for superiority was used to test the one-sided hypothesis that treatment with Amlodipine+Celecoxib improved creatinine clearance to a greater degree than Amlodipine+Placebo. Note, although the alpha was not met for the DBP24h efficacy endpoint of the serial gate-keeping strategy, creatinine clearance was still evaluated for informational purposes and the results are presented here.

[11] - Creatinine clearance increased from baseline to end of study in both arms; however, the superiority of Amlodipine+Celecoxib over Amlodipine+Placebo was not demonstrated. See further evaluation of renal function under serum creatinine outcome.

## Secondary: Incidence of Treatment Emergent Adverse Events

| End point title | Incidence of Treatment Emergent Adverse Events |
|---|---|

End point description:

Treatment emergent adverse events (TEAEs) included any untoward medical occurrence that initiated or worsened after the first dose of study drugs and within 14 days of the last dose of study drugs.

| End point type | Secondary |
|---|---|

End point timeframe:

1 month

| End point values | Amlodipine+Celecoxib | Amlodipine+Placebo | Placebo+Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48 | 49 | 8 | |
| Units: Subjects | | | | |
| number (not applicable) | 35 | 32 | 6 | |

## Statistical analyses

| Statistical analysis title | StatsAnalysis1 Incidence of Treatment Emergent AEs |
|---|---|
| Comparison groups | Amlodipine+Celecoxib v Amlodipine+Placebo v Placebo+Placebo |
| Number of subjects included in analysis | 105 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[12] |
| P-value | = 0.675 |
| Method | Chi-squared |

Notes:

[12] - Differences in the incidence of TEAEs between treatment arms were evaluated using Chi-square test.

| Statistical analysis title | StatsAnalysis2 Incidence of Treatment Emergent AEs |
|---|---|
| Comparison groups | Amlodipine+Celecoxib v Amlodipine+Placebo |
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[13] |
| P-value | = 0.555 |
| Method | Regression, Logistic |

Notes:

[13] - Amlodipine+Celecoxib and Amlodipine+Placebo arms were compared by logistic regression, where TEAE (1=at least one TEAE occurred for the subject; 0=otherwise) as dependent variable and treatment as fixed effect.

## Secondary: Non-transformed Plasma Concentration of Amlodipine

| End point title | Non-transformed Plasma Concentration of Amlodipine[14] |
|---|---|

End point description:

Pharmacokinetic (PK) population = all subjects enrolled at an Investigational Site with ultraviolet- (UV-) shielded lights who had blood drawn on Day 14,
24 hours ± 1 hour after receiving the final dose of study drugs for the measurement of plasma amlodipine concentration; only treatment arms that included amlodipine were included in the analyses.

| End point type | Secondary |
|---|---|

End point timeframe:

24 hours post-dose on Day 14

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per protocol, no "amlodipine" PK statistical analyses were performed for the PK subjects in the placebo + placebo arms (i.e., the arms that did not receive amlodipine). No subjects in these arms had detectable levels of amlodine in their plasma, and as such, PK analysis was not possible for these subjects.

| End point values | Amlodipine+Celecoxib | Amlodipine+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 | 20 | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 15.9 (± 5.72) | 18.3 (± 7.21) | | |

## Statistical analyses

| Statistical analysis title | Nontransformed PlasmaConcentration of Amlodipine |
|---|---|
| Statistical analysis description: | |
| For this analysis, all values below the limit of quantification were treated as 0. | |
| Comparison groups | Amlodipine+Celecoxib v Amlodipine+Placebo |
| Number of subjects included in analysis | 43 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.226 |
| Method | t-test, 2-sided |

## Secondary: Log-transformed Plasma Concentration of Amlodipine

| End point title | Log-transformed Plasma Concentration of Amlodipine[15] |
|---|---|
| End point description: | |

PK population = all subjects enrolled at an Investigational Site with ultraviolet- (UV-) shielded lights who had blood drawn on Day 14, 24 hours ± 1 hour after
receiving the final dose of study drugs for the measurement of plasma amlodipine concentration; only treatment arms that included amlodipine were included in the analyses.

| End point type | Secondary |
|---|---|
| End point timeframe: | |

24 hours post-dose on Day 14

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per protocol, no "amlodipine" PK statistical analyses were performed for the PK subjects in the placebo + placebo arms (i.e., the arms that did not receive amlodipine). No subjects in these arms had detectable levels of amlodine in their plasma, and as such, PK analysis was not possible for these subjects.

| End point values | Amlodipine+Celecoxib | Amlodipine+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 | 20 | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 2.7 (± 0.44) | 2.8 (± 0.36) | | |

## Statistical analyses

| Statistical analysis title | Log-transformed Plasma Concentration of Amlodipine |
|---|---|

Statistical analysis description:

For this analysis, all values below the limit of quantification (BLQ) were treated as 0.04 ng/mL. Assignment of BLQ values to a nonzero number allowed computation of the log transformation. The selection of 0.04 ng/mL was based on the lower limit of quantification of the validated bioanalytical method (0.05 ng/mL) and selecting the next lowest number at the hundredth decimal place.

| Comparison groups | Amlodipine+Celecoxib v Amlodipine+Placebo |
|---|---|
| Number of subjects included in analysis | 43 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.215 |
| Method | t-test, 2-sided |

# Adverse events

## Adverse events information

Timeframe for reporting adverse events:

1 month; TEAEs include any untoward medical occurrence that initiated or worsened after the first dose of study drugs and within 14 days of the last dose of study drugs.

Adverse event reporting additional description:

Subjects were instructed to report all adverse events (AEs) experienced during the study, and subjects were assessed for the occurrence of AEs throughout the study. Secondary safety assessments included physical examination, body weight, vital signs, orthostatic hypotension evaluations, ECG, hematology, serum chemistry, and urinalysis.

| Assessment type | Systematic |
|---|---|

## Dictionary used

| Dictionary name | MedDRA |
|---|---|
| Dictionary version | 19.1 |

## Reporting groups

| Reporting group title | Amlodipine+Celecoxib |
|---|---|

Reporting group description:

Over-encapsulated 10 mg amlodipine besylate tablet + over-encapsulated 200 mg celecoxib capsule once a day for two weeks

Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Over-encapsulated 200 mg celecoxib capsule: Over-encapsulated 200 mg celecoxib capsule once a day for two weeks

| Reporting group title | Amlodipine+Placebo |
|---|---|

Reporting group description:

Over-encapsulated 10 mg amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

| Reporting group title | Placebo+Placebo |
|---|---|

Reporting group description:

Matched placebo capsule for over-encapsulated amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Matched placebo capsule for over-encapsulated amlodipine besylate tablet: Matched placebo capsule for over-encapsulated amlodipine besylate tablet once a day for two weeks

| Serious adverse events | Amlodipine+Celecoxib | Amlodipine+Placebo | Placebo+Placebo |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 49 (0.00%) | 0 / 8 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Amlodipine+Celecoxib | Amlodipine+Placebo | Placebo+Placebo |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 25 / 48 (52.08%) | 23 / 49 (46.94%) | 6 / 8 (75.00%) |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | 2 / 49 (4.08%) | 2 / 8 (25.00%) |
| occurrences (all) | 2 | 2 | 2 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 5 / 48 (10.42%) | 9 / 49 (18.37%) | 2 / 8 (25.00%) |
| occurrences (all) | 10 | 10 | 3 |
| Dizziness | | | |
| subjects affected / exposed | 3 / 48 (6.25%) | 1 / 49 (2.04%) | 0 / 8 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Lethargy | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 49 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 7 / 48 (14.58%) | 4 / 49 (8.16%) | 0 / 8 (0.00%) |
| occurrences (all) | 7 | 5 | 0 |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 49 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Fatigue | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | 0 / 49 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 2 | 0 | 1 |
| Feeling cold | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 49 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Feeling hot | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 3 / 49 (6.12%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 6 | 0 |
| Pain | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 49 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 2 |
| Eye disorders | | | |
| Eye swelling | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 49 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 49 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 49 (2.04%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 1 | 1 |
| Flatulence | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 49 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 2 / 49 (4.08%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 2 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 2 / 49 (4.08%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 2 | 1 |
| Rash | | | |
| subjects affected / exposed | 3 / 48 (6.25%) | 0 / 49 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Joint swelling | | | |
| subjects affected / exposed | 10 / 48 (20.83%) | 9 / 49 (18.37%) | 1 / 8 (12.50%) |
| occurrences (all) | 12 | 13 | 1 |
| Arthralgia | | | |

| | 0 / 48 (0.00%) | 3 / 49 (6.12%) | 0 / 8 (0.00%) |
|---|---|---|---|
| subjects affected / exposed | 0 / 48 (0.00%) | 3 / 49 (6.12%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 8 | 0 |

**Infections and infestations**

| Rhinitis | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 49 (2.04%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 1 | 1 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 0 / 49 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |

**Metabolism and nutrition disorders**

| Increased appetite | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 48 (2.08%) | 0 / 49 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 0 | 1 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol?  No

### Interruptions (globally)

Were there any global interruptions to the trial?  No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| No limitations |
| --- |

Notes: